Citation:

Persad VL, Van den Hof MC, Dubé JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *Canadian Medical Association Journal.* 2002; 167: 241-245.

PubMed ID: 12186168

Study Design:

Retrospective cohort study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To evaluate the annual incidence of all open neural tube defects (NTDs), including those occurring in stillbirths and terminated pregnancies, in Nova Scotia over a 10-year period (1991 to 2000). The period spans times before and after folic acid supplementation initiatives and before and after folic acid fortification of grain products was implemented.

Inclusion Criteria:

- Live birth, stillbirth or terminated pregnancy recorded between January 1, 1991 and December 31, 2000 in Nova Scotia
- Registration in the population-based Nova Scotia Atlee Perinatal Database (for births) or the population-based Fetal Anomaly Database (for terminated pregnancies).

Exclusion Criteria:

Live birth, stillbirth or terminated pregnancy prior to January 1, 1991 or after December 31, 2000 or outside Nova Scotia.

Description of Study Protocol:

Recruitment

- For all live births and stillbirths during the study period, hospital records were abstracted into the Nova Scotia Atlee Perinatal Database by trained registry personnel
- All terminations of pregnancies affected by fetal anomalies in Nova Scotia were performed at a single tertiary care center. A trained person entered information on antenatal findings and final diagnosis through postmortem pathologic examination or gross examination of fetal remains.

Design

A retrospective cohort design was used to analyze incidence of NTDs in periods before and after folic acid supplementation initiatives and before and after folic acid fortification implementation in Nova Scotia over 10 years.

Intervention

- In 1994, Canada issued recommendations for folic acid supplementation before conception
- In 1998, Canada mandated folic acid fortification of grain products.

Statistical Analysis

Incidence rates were computed as the number of open NTDs, spina bifida (SB) and anencephaly (AN) cases occurring in live births, stillbirths, and terminated pregnancies.

Data Collection Summary:

Timing of Measurements

Data were abstracted for the appropriate registry from hospital records from 1991 to 2000.

Dependent Variables

Open NTDs, including spina bifida and anencephaly:

- Diagnosis for live births and stillbirths was not described
- Among terminated pregnancies, diagnosis was based on postmortem pathologic examination or gross examination of fetal remains.

Independent Variables

- Canada's recommendation for preconceptional folic acid supplementation in 1994: 1991 to 1994 vs. 1995 to 1997 periods were compared
- Canada's mandatory folic acid fortification of grain products in 1998: 1991 to 1997 vs. 1998 to 2000 periods were compared.

Description of Actual Data Sample:

- N=107,851 live births, stillbirths, and terminated pregnancies
- *Location:* Nova Scotia, Canada.

Summary of Results:

Year	Total N Live Births, Stillbirths, and Terminated Pregnancies	Open NTDs				Spina Bifida				Anencephaly			
		N in Live Births and Stillbirths	N in Terminated Pregnancies	Total N	Incidence per 1000 Births	N in Live Births and Stillbirths	N in Terminated Pregnancies	Total N	Incidence per 1000 Births	N in Live Births and Stillbirths	N in Terminated Pregnancies	Total N	Incidence per 1000 Births
Pre-supplementation													
1991	11,933	18	12	30	2.51	11	5	16	1.34	7	6	13	1.09
1992	12,076	17	13	30	2.48	12	6	18	1.49	3	7	10	0.83
1993	11,715	14	16	30	2.56	11	5	16	1.37	2	11	13	1.11
1994	11,340	12	18	30	2.64	10	8	18	1.59	2	9	11	0.97
Post-supplementation and Pre-fortification													
1995	10,913	5	18	23	2.11	2	12	14	1.28	2	6	8	0.73
1996	10,739	13	25	38	3.54	9	16	25	2.33	2	8	10	0.93
1997	10,125	8	14	22	2.17	6	6	12	1.19	2	6	8	0.79
Post-fortification													
1998	9,785	7	7	14	1.43	5	3	8	0.82	1	4	5	0.51
1999	9,676	1	10	11	1.14	1	4	5	0.52	0	3	3	0.31

2000	9,549	1	8	9	0.94	1	4	5	0.52	0	3	3	0.31
Total	**107,851**	96	141	239	2.22	68	69	137	1.27	21	63	84	0.78

Comparing pre-supplementation vs. post-supplementation periods (1991 to 1994 vs. 1995-1997), there were no significant changes in incidence:

- There was no change in the total annual incidence of open NTDs
- Mean annual incidence of NTDs was 2.55 per 1,000 births during 1991 to 1994 and 2.61 per 1,000 births during 1995 to 1997 (RR=1.02; 95% CI, 0.77 to 1.35, P=0.87)
- Mean annual incidence for SB did not change significantly (1.44 and 1.60 per 1,000 births, respectively for each period mentioned above (RR=1.11, 95% CI: 0.79-1.60, P=0.64)
- Mean annual incidence for anencephaly did not change significantly (1.00 to 0.82 per 1,000 births) (RR=0.82, 95% CI: 0.51 to 1.32, P=0.49).

Comparing pre-fortification vs. post-fortification periods (1991 to1997 vs. 1998 to 2000); incidence declined:

- Open NTDs fell 54%, from 2.58 per 1,000 births on average during 1991 to 1997 to 1.17 per 1,000 births during 1998 to 2000 (RR=0.46, 95% CI: 0.32 to 0.66, P<0.001)
- Mean annual incidence of SB decreased from 1.51 per 1,000 births before to 0.62 per 1,000 births after folic acid fortification (RR=0.40, 95% CI: 0.25-0.67, P<0.001)
- Mean annual inicidence of anencephaly decrease from 0.93 to 0.38 per 1,000 births after folic acid fortification (RR=0.41, 95% CI: 0.22 to 0.77, P=0.004).

Author Conclusion:

- In the years before fortification, public education on the importance of folic acid supplementation had no significant effect on the incidence of open NTDs, presumably due to an inability to change women's behavior in taking preconceptual supplements
- Our results suggest that folic acid fortification was successful; there was a highly significant drop in the total incidence of open NTDs as well as spina bifida and anencephaly separately, taking into account all affected pregnancies (live births, stillbirths and terminated pregnancies)
- The greater than anticipated reduction in open neural tube defects could be explained by a higher background incidence in Nova Scotia, so the population may have been more sensitive to the influence of folic acid
- If the observed decline (54%) is verified in other geographic areas, it may suggest that the current level of fortification is adequate and that the controversial call for higher-dose fortification should await further studies.

Reviewer Comments:

- *Author-noted limitations:*
  - *Arbitrary definitions for the supplementation and fortification periods, as the beginning of the supplementation period is poorly defined*
  - *A cause-effect relationship between supplementation and fortification strategies and the changes in incidence of NTDs is highly suggestive but cannot be proved*
- *It is unclear whether births outside the hospital setting may have altered the study findings, since only hospital births or pregnancy terminations were included in the registries*
- *Since demographic, health and behavior variables were not reported, it is possible that declines in NTDs could be due to population changes rather than policy implementation. For example, higher-risk groups may have been moving out of Nova Scotia, women may have increased their dietary folate intake independent of folic acid fortification or education strategies may have lagged sufficiently to make behavior changes appear in the post-fortification period.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	???
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	No
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes

	5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
	5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
	5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
	5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
	5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**		Yes
	6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
	6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
	6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
	6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
	6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
	6.6.	Were extra or unplanned treatments described?	N/A
	6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
	6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	No
	10.2.	Was the study free from apparent conflict of interest?	Yes